## REMARKS/ARGUMENTS

No amendments are made to the claims.

### *Claim Rejections 35 U.S.C. § 103*

Claims 3-4, 12-13, 15-18, 22-26, and 30 were rejected as allegedly being obvious over Burk (US 6,531,504) in view of JP63002972. Applicants respectfully disagree.

*KSR International Co. v. Teleflex Inc.*, endorsed the *Graham* analysis for determining obviousness. 127 S.Ct. 1727, 1739 (U.S. 2007). According to the MPEP, *Graham* requires Examiners to (A) Determine the scope and contents of the prior art; (B) Ascertain the differences between the prior art and the claims in issue; (C) Resolve the level of ordinary skill in the pertinent art; and (D) Evaluate evidence of secondary considerations. MPEP 2141(I). Applying the *Graham* analysis to the prior art shows that the claims are not prima facie obvious.

### Level of Skill in the Art

The Office should "occupy the mind of one skilled in the art"[1] to find out what that person would do in a given situation. Here, the person of ordinary skill in the art is a medicinal chemist. Therefore, the Office should view the reference as if it were a medicinal chemist in February of 2003, which is the priority date for this application.

[1] *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

**The Scope and Contents of the Prior Art**

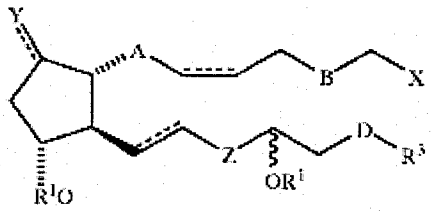
Hindsight

The prior art must not have been selected by the use of hindsight.[2] In this case, the Office cited references provided by the Applicants which were obtained by either a prior art search made by the Applicants based upon the claims or by a prior art search made by a foreign patent office based upon the claims. These are both hindsight selections of the prior art. However, the Office has not provided any reason, other than their relationship to the claims, why a person of ordinary skill in the art would have selected Burk and JP63002972 for further research. Thus, the references were selected based upon hindsight, and the rejection is improper.

Teachings and suggestions in the Prior Art

Burk

Burk teaches compounds having the structure below.

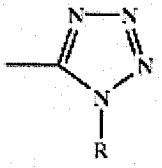



[2] *Pentec, Inc. v. Graphic Controls Corp.* 776 F.2d 309, 313 (Fed. Cir.1985).

A and B are $CH_2$;

D represents a covalent bond or $CH_2$, O, S or NH;

X is $CO_2R$, $CONR_2$, $CH_2OR$, $P(O)(OR)_2$, $CONRSO_2R$ $SONR_2$ or



Y is O, OH, $OCOR^2$, halogen or cyano;

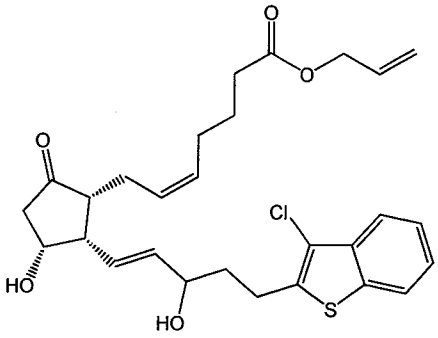
Z is $CH_2$ or a covalent bond;

R is H or $R^2$;

$R^1$ is H, $R^2$, phenyl, or $COR^2$;

$R^2$ is $C_1$–$C_5$ lower alkyl or alkenyl and $R_3$ is benzothienyl, benzofuranyl, naphthyl or substituted derivatives thereof, wherein the substituents maybe selected from the group consisting of $C_1$–$C_5$ alkyl, halogen, $CF_3$, CN, $NO_2$, $NR_2$, $CO_2R$ and OR.

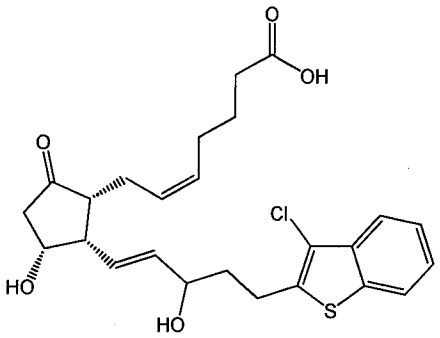
The reference discloses that "[c]ompounds 6(a) and 7(a) are examined and show a pronounced ocular hypotensive effect."[3] Compounds 6(a) and 7(a) are:[4]



(Z)-7-{(1R,2R,3R)-2-[(E)-(S)-5-(3-Chlorobenzo[b]thiophen-2-yl)-3-hydroxypen t-1-enyl]-3-hydroxy-5-oxocyclopentyl}hept-5-enoic acid allyl ester (6a)

[3] Column 7, lines 65-66.

[4] Column 4 lines 53-58. The structures were not in Burk, but were generated from the names.




(Z)-7-{(1R,2R,3R)-2-[(E)-(S)-5-(3-Chlorobenzo[b]thiophen-2-yl)-3-hydroxypen t-1-enyl]-3-hydroxy-5-oxocyclopentyl}hept-5-enoic acid (7a)

The other specific compounds disclosed in Burk are:

(Z)-7-{(1R,2R,3R)-2-((E)-(S)-5-Benzo[b]thiophen-2-yl-3-hydroxypent-1-enyl]- 3-hydroxy-5-oxocyclopentyl}hept-5-enoic acid allyl ester (6b)

(Z)-7-{(1R,2R,3R) 2-((E)-(S)-5-Benzo[b]thiophen-2-yl-3-hydroxypent-1-enyl]-3-hydroxy-5-oxocyclopentyl}hept-5-enoic acid (7b)

(Z)-7-{(1R,2R,3R)-3-Hydroxy-2-((E)-(S)-3-hydroxy-5-naphthalen-2-yl-pent-1-enyl)-5-oxocyclopentyl}hept-5-enoic acid allyl ester (6c)

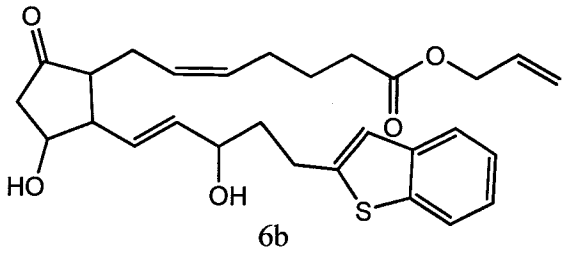
(Z)-7-{(1R,2R,3R)-3-Hydroxy-2-((E)-(S)-3-hydroxy-5-naphthalen-2-yl-pent-1-enyl)-5-oxocyclopentyl}hept-5-enoic acid (7c)

(Z)-7-{(1R,2R,3R)-2-[(E)-(S)-5-(4-Bromo-2,5-dimethylthiophen-3-yl)-3-hydroxypent-1-enyl]-3-hydroxy-5-oxocyclopentyl}hept-5-enoic acid allyl ester (6d) and

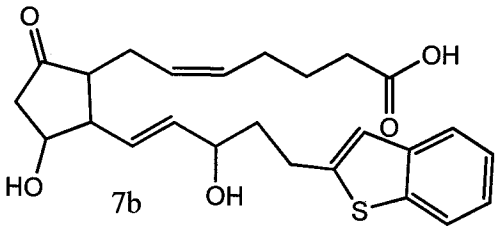
(Z)-7-{(1R,2R,3R)-2-[(E)-(S)-5-(4-Bromo-2,5-dimethylthiophen-3-yl)-3-hydroxypent-1-enyl]-3-hydroxy-5-oxocyclopentyl}hept-5-enoic acid (7d).[5]

These names correspond to the structures below.

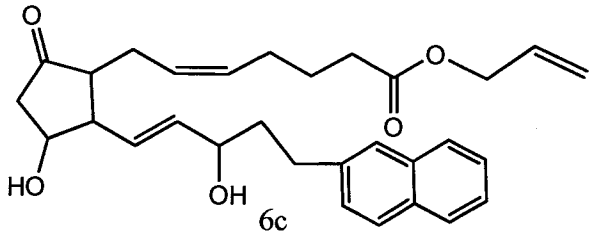
[5] See claim 1.



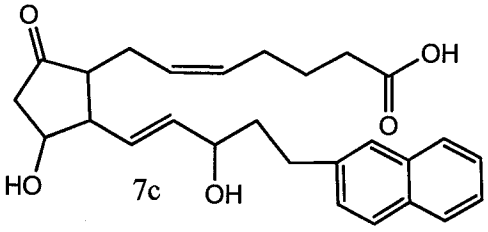

6b



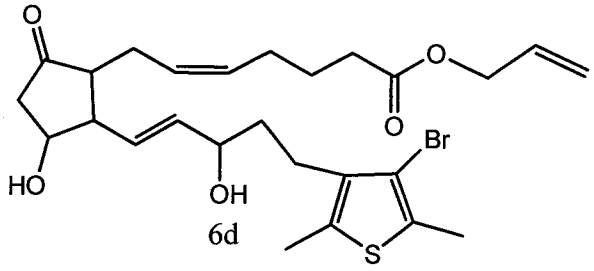

7b



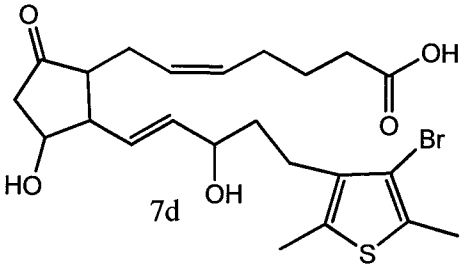

6c




7c



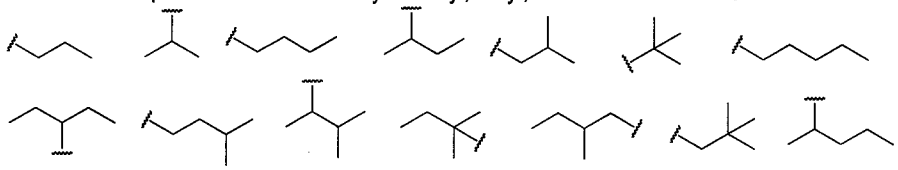

6d




7d

Thus, all the variation in these specific examples is in the aryl group at $R^3$. The following substituents are disclosed for the aryl or heteroaryl ring of $R^3$: $C_1$-$C_5$ alkyl, halogen, $CF_3$, CN, $NO_2$, $NR_2$, $CO_2R$ and OR (R is H, $C_{1-5}$ alkyl or alkenyl). This presents a nearly limitless[6] number of compounds that may be prepared without any need to go beyond the disclosure of Burk. Furthermore, the synthetic pathway presented in Figure 1 does not provide any indication as to how a person would go outside the scope of Burk. The most obvious place to

[6] There are 16 possibilities for $C_{1-5}$ alkyl: methyl, ethyl, and the structures below.



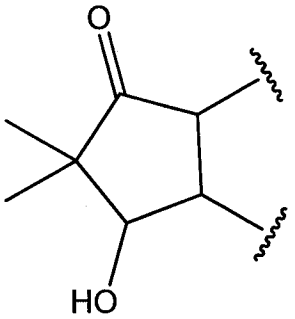
Thus, $CO_2R$ and OR present 17 possibilities each, and $NR_2$ presents 272 possibilities ($17^2$-17).
There are 4 commonly used halogens (F, Cl, Br, I). Thus, disregarding alkenyl, there are 312 possible substituents on $R^3$ (16 + 17 + 17 + 272 + 4). For the thienyl of 6d and 7d, this presents over 30 million ($312^3$) possible combinations of substituents. The possible combinations with the addition of naphthyl and benzothienyl are far greater.

vary the compounds is at –D-$R^3$, which is added separately from the rest of the molecule in the first step of the synthesis.

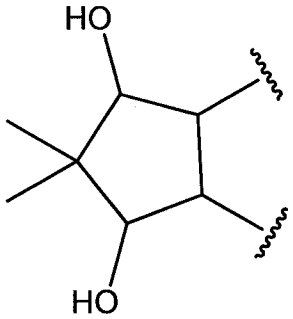
Therefore, there is nothing in Burk to suggest going beyond the scope of its disclosure.

JP63002972

Even if Burk did suggest going beyond the scope of its disclosure, this reference is not where a person of ordinary skill in the art would go for suggestions to further modify Burk. The general belief in the art at the time of filing was that prostaglandin derivatives having the substitution of this reference, depicted below, were inactive or had very poor activity.




Protaglandin E analogs
Inactive or poor activity




Prostaglandin F analogs
Inactive

Hamon[7] teaches "[w]hen tested on the isolated rat uterus compounds (11a) and (11b) [Prostaglandin E analogs] showed weak muscular agonist activity (about 1/1000 that of PG $F_{2\alpha}$); at the same concentration the 15-epimers (12a) and (12b) [diastereomers of 11a and 12b] were inactive."[8] Furthermore, Plantema[9] refers to Hamon, observing that "only (28) showed very weak agonist activity while (32) was inactive."[10] Finally, Plantema published a synthesis of the F analogs[11] and observed "[i]n a preliminary biological investigation, none of the

[7] *Tet. Lett*, No. 3, 211-214 (1976)
[8] *Id.* at Note 10.
[9] *J.C.S. Perkin I*, 1978, 304
[10] Id. at 306.
[11] *Recl. Trav. Chim. Pays-Bas* 102, 268-275 (1983)

PG analog[s] showed interesting activities in vitro in either the rat uterus test or the superfusion test."[12] Therefore, the prior art clearly teaches away from the combination of Burk with this reference.

At the time of filing, a person of ordinary skill in the art, being aware of the references cited, would observe that this reference was filed as a patent application in only Japan in no other countries. This would lead the person of ordinary skill to conclude that the patent application was not filed in any other countries because the compounds had disappointing performance. Furthermore, this reference was published in 1988, about 15 years before the present application, and the Office has provided no references in the intervening years suggesting the dimethyl substitution of this reference. This strongly suggests that, based upon the teachings explained above, those of ordinary skill in the art had concluded that dimethyl substitution in this particular position of prostaglandins would not yield useful compounds. As a result, it appears that this line of work had been abandoned for 15 years by the time the present application was filed. Therefore, the prior art does not fairly suggest the modification of Burk using this reference.

**Ascertaining the Difference Between the Prior Art and the Claims**

Burk does not disclose or suggest the dimethyl substitution of the present application. As explained above, the prior art teaches away from combination of JP63002972 with Burk because it teaches that dimethyl substitution in the natural prostaglandin E and F compounds renders the compounds inactive. Therefore, the claims are not obvious.

**Secondary Considerations**

Since the claims are not prima facie obvious based on the prior art, Applicants need not show secondary considerations.

[12] *Id.* at 272 (under "Biological Activity").

In light of the arguments made herein, Applicants respectfully request that the rejections be withdrawn and the application be allowed to issue.

No fee is believed due in connection with this communication. However, if applicant is in error please charge Deposit Account 01-0885 for any fees related to this response.

Respectfully submitted,

Dated: August 19, 2008

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Enclosures:

1. *Tet. Lett*, No. 3, 211-214 (1976)
2. *J.C.S. Perkin I*, 1978, 304
3. *Recl. Trav. Chim. Pays-Bas* 102, 268-275 (1983)